EDITORIAL

Myocardial gene and cell delivery

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Although we now have the tools to introduce vectors and stem cells into specific myocardial locations, these devices are yet to be matched by comparable advances in molecular virology, cell biology, and our understanding of the pathophysiology of ischaemic heart disease

Basic and clinical studies involving gene therapy (the introduction of nucleic acid into cells to achieve a therapeutic effect) and/or cell therapy (the introduction of live cells to achieve a therapeutic effect) are increasing exponentially. Their attraction lies in the apparent simplicity of translating basic findings into a clinical benefit. In addition, the diseases being addressed have become increasingly ambitious, progressing from the treatment of single gene disorders, such as lipoprotein receptor deficiency, to the modulation of complex pathological entities such as restenosis, heart failure, and myocardial infarction. In all these situations there is a need to deliver the therapy to a specific location within the cardiovascular system and then measure its effect.

The report by Barbash and colleagues[1] in the current issue is an elegant illustration of how a single technique, magnetic resonance imaging (MRI), can be used to target gene or cell delivery to a specific myocardial region. In addition, although image acquisition was not gated to the cardiac cycle, the technique still had sufficient spatial resolution to monitor the alterations in left ventricular (LV) cross sectional area after myocardial infarction. The combined ability of MRI to target and visualise gene and/or cell delivery as well as monitor the consequent changes in the process of LV remodelling suggest that it may be uniquely placed. In this editorial we shall address some of the issues surrounding myocardial gene and cell therapy and the techniques that are available that can both guide delivery and measure its consequences.

ROUTES TO CELL IMPLANTATION

Routes to achieve myocardial transfection or cell implantation to a pre-specified region include intramyocardial injection, from either the epicardial or endocardial surface, or intracoronary infusion. More novel approaches include the use of sonicated microbubbles to release vector[2] or retrograde perfusion of the coronary veins.[3] Progenitor cell therapy raises the prospect of using these routes not only to replace or augment diseased cells within the heart, but also allows these cells to act as host to a therapeutic gene introduced by ex vivo manipulation.[4] The myocardium is relatively resistant to transfection/cell engraftment. In addition the therapeutic agents are often toxic in non-diseased myocardium and non-cardiac tissue; these shortcomings unite to mandate that delivery is localised to the diseased target area with little systemic spillover. In the absence of direct exposure of the heart this is most easily accomplished by endocardial delivery with MRI, as discussed by Barbash and colleagues,[1] or electroanatomical mapping.[5–7]

MRI offers the advantages of precisely discerning local myocardial segmental motion, extent of hypoperfusion with early/late gadolinium enhancement, and also viability with dobutamine stress. The small intra- and inter-observer variability in measurement of LV volume and mass mean that only a small sample size is required to detect a significant difference in cardiac dimensions—that is, only 12 patients to discern a 10 ml change in LV end systolic volume.[8] This has important implications in the design of gene/cell therapy protocols. By careful registration of the site of intramyocardial injection through combined *x* ray and MRI imaging the exact location of vector delivery can be precisely determined, facilitating tracking of the relevant site for therapeutic response or even biopsy to assess histological changes at a later date. In addition, a number of studies, including that from Barbash and Leor's group in this issue,[1] demonstrate that MRI using either iron flurophores or gadolinium labelling can now track stem cells. This provides invaluable information about cell distribution and survival.[9 10]

ELECTROANATOMICAL INFORMATION

In addition to MRI, the NOGA and Ensite 3000 systems can provide complementary electroanatomical information. The endocardial potential of a specific segment has been demonstrated to correlate with viability of the local myocardial tissue. The NOGA system has been validated in animal and human studies investigating the mechanics and electrical properties of the left ventricle.[5] This mapping and navigation system comprises a miniature passive magnetic field sensor, an external ultralow magnetic field emitter (location pad), and a processing unit. The catheter tip incorporates standard electrodes that allow recording of unipolar and bipolar signals and a location sensor. The location pad is fixed beneath the operating table and generates magnetic fields that code the mapping space around the chest with spatial and temporal mapping characteristics. Thus the location and orientation of the catheter can be determined in 6 degrees of freedom. The catheter position can then be determined at fixed points in the cardiac cycle and thus a map of regional contractility constructed. Simultaneous measurement of the

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endocardial electrical potential allows excitation and contraction to be measured in individual segments of the LV.

This system has now been employed in patients both in electrophysiological procedures and in the assessment of myocardial viability in the laser revascularisation trials of the last decade. Fuchs has demonstrated that a significant difference exists in the amplitude of the endocardial potentials generated by myocardial segments that are triaged on the basis of fixed, reversible, or normal, perfusion by dual isotope imaging.[6] Thus, this system can direct gene transfer to a specific and mapped myocardial site. In addition it can also assess the effect of local gene transfer on myocardial viability (perfusion) and contractility by returning exactly to the same location at a later date. Indeed segments of hibernating myocardium (that is, electrically active but non-contractile) can also be evaluated to examine whether they become mechanically active post gene transfer.[7]

NON-CONTACT MAPPING

A non-contact mapping approach is utilised by the Ensite 3000 system (Endocardial Solutions Inc, St Paul, Minnesota, USA). The system comprises a multielectrode array mapping catheter placed in the LV to reconstruct endocardial potentials employing the inverse solution method and utilises a locator signal from a standard steerable ablation catheter to construct LV chamber geometry,[11] also enabling cell/vector delivery. This endocardial non-contact mapping system could be combined with MRI to present detailed LV geometric information combined with local endocardial potential data enabling precise gene delivery to sites of ischaemic and hibernating myocardium.

Although ''the kit'' exists to deliver gene transfer vectors to a precise location, the transfection of cardiac myocytes is proving to be remarkably difficult. We have evaluated a number of vectors by both direct intramyocardial injection and intracoronary infusion in an in vivo rabbit model.[12] Direct intramyocardial injection of plasmid DNA only results in $< 1\%$ myocyte transfection. Adenoviral vectors are the most effective, resulting in transfection efficiencies of up to 30% in the myocardium immediately adjacent to the needle track. However, they are associated with a pronounced inflammatory response leading to a significant reduction in gene expression within two weeks. Intracoronary infusion offers a less invasive approach. However, in our hands, the coronary endothelium and rapid coronary transit conspire to frustrate transfection by this technique. In an attempt to overcome these barriers investigators have increased coronary permeability with VEGF, bradykinin, serotonin,[13] adenosine or calcium free buffer, prolonged intracoronary dwell time using hyperoxygenated perfluocarbons, and increased intracapillary pressure by simultaneous occlusion of aorta and main pulmonary artery. The latter approach was the most successful in our hands.[12] In part these limitations might be overcome by advances in molecular virology which are bringing safer and more efficient viruses encoding transgenes that are more tightly regulated by the pathophysiological environment.[14]

In summary advances in solid state physics, as evidenced by the manuscript from Barbash and Leor's group in the current issue,[1] are providing us with the tools to introduce vectors and stem cells into specific myocardial locations and then monitor consequent physiological effects. However, these advances are yet to be matched by comparable advances in molecular virology, cell biology, and our understanding of the pathophysiology of ischaemic heart disease.

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REFERENCES

1 **Barbash IM**, Leor J, Feinberg MS, *et al.* Interventional magnetic resonance imaging for guiding gene and cell transfer in the heart. *Heart* 2004;**90**:87–91.
2 **Beeri R**, Guerrero JL, Supple G, *et al.* New efficient catheter-based system for myocardial gene delivery. *Circulation* 2002;**106**:1756–9.
3 **Gerber TC**, Kantor B, Keelan PC, *et al.* The coronary venous system: an alternate portal to the myocardium for diagnostic and therapeutic procedures in invasive cardiology. *Curr Interv Cardiol Rep* 2000;**2**:27–37.
4 **Mangi AA**, Noiseux N, Kong D, *et al.* Mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infarcted hearts. *Nature Med* 2003;**9**:1195–201.
5 **Kornowski R**, Fuchs S, Leon MB. Detection of myocardial viability in the catheterization laboratory using the Biosense-guided electromechanical mapping system. *Int J Cardiovasc Intervent* 1999;**2**:125–8.
6 **Fuchs S**, Hendel RC, Baim DS, *et al.* Comparison of endocardial electromechanical mapping with radionuclide perfusion imaging to assess myocardial viability and severity of myocardial ischemia in angina pectoris. *Am J Cardiol* 2001;**87**:874–80.
7 **Kawamoto A**, Tkebuchava T, Yamaguchi J-I, *et al.* Intramyocardial transplantation of autologous endothelial progenitor cells for therapeutic neovascularization of myocardial ischemia. *Circulation* 2003;**107**:461–8.
8 **Bellenger NG**, Davies LC, Francis JM, *et al.* Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2000;**2**:271–8.
9 **Hill JM**, Dick AJ, Raman VK, *et al.* Serial cardiac magnetic resonance imaging of injected mesenchymal stem cells. *Circulation* 2003;**108**:1009–14.
10 **Kraitchman DL**, Heldman AW, Atalar E, *et al.* In vivo magnetic resonance imaging of mesenchymal stem cells in myocardial infarction. *Circulation* 2003;**107**:2290–3.
11 **Schilling RJ**, Peters NS, Davies DW. Simultaneous endocardial mapping in the human left ventricle using a noncontact catheter: comparison of contact and reconstructed electrograms during sinus rhythm. *Circulation* 1998;**98**:887–98.
12 **Wright MJ**, Wightman LM, Latchman DS, *et al.* In vivo myocardial gene transfer: optimization and evaluation of intracoronary gene delivery in vivo. *Gene Ther* 2001;**8**:1833–9.
13 **Donahue JK**, Kikkawa K, Thomas AD, *et al.* Acceleration of widespread adenoviral gene transfer to intact rabbit hearts by coronary perfusion with low calcium and serotonin. *Gene Ther* 1998;**5**:630–4.
14 **Vincent KA**, Shyu KG, Luo Y, *et al.* Angiogenesis is induced in a rabbit model of hindlimb ischemia by naked DNA encoding an HIF-1{alpha}/VP16 hybrid transcription factor. *Circulation* 2000;**102**:2255–61.